High-Throughput, Fully Automated Analysis of USP<467> Residual Solvents Using Headspace-MRR

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Introduction

USP <467> recommends static headspace GC (SH-GC) for residual solvent analysis. Yet, many important solvents, including low-volatility compounds, acids and amines remain analytically challenging.

Molecular Rotational Resonance (MRR) spectroscopy directly identifies volatile molecules in mixtures by their unique gas-phase rotational spectra, providing unambiguous ID and reliable quantitation without chromatography.

Here we demonstrate fully automated headspace–MRR method for high-throughput analysis of GC-unfriendly residual solvents in pharmaceutical substances, expanding analytical coverage beyond conventional SH-GC.

MRR Applications

Structure verification when standards are not available
- J. L. Neill et al., *Org. Process Res. Dev.*, **2019**, 23 (5), 1046.
- J.L. Neill et al., *Anal Sci Adv.* **2023**, 4, 204

Direct analysis of stereo- and regio-isomer mixtures
- J. L. Neill et al., *J. Pharm. Biomed. Analysis*, **2020**, 189, 113474
- L.A. Joyce et al., *Chem. Sci.*, **2020**, 11, 6332
- R.E. Sonstrom et al., *Chirality*, **2022**, 34 (1), 114
- J.L. Neill et al., *Anal Sci Adv.* **2023**, 4, 204

Online, highly-selective reaction monitoring
- J. L. Neill et al., *Org. Process Res. Dev.*, **2019**, 23 (5), 1046.
- A.A. Byars et al., *Precis. Chem.*, **2024**, 2, 57

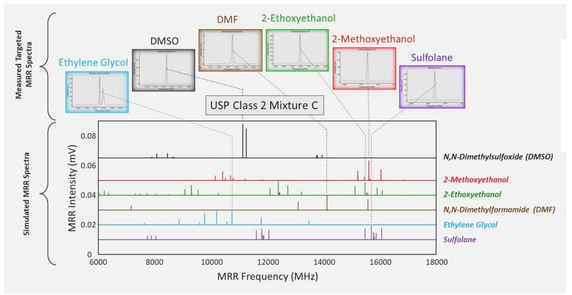
Site-specific isotope analysis, deuterated isotopomers
- Z.P. Vang et al., *J. Am. Chem. Soc.*, **2021**, 143 (20), 7707
- M.D. Mills et al., *Angew. Chemie*, **2022**, 61 (33), e202207275
- R.E Sonstrom et al., *Org. Process Res. Dev.*, **2023**, 27 (7), 1185

GC-Unfriendly Volatile Impurities
- A.V. Mikhonin et al., *USP Stimuli Article*, USP-NF, March 3, **2025**
- Formaldehyde, ethylene oxide and acetaldehyde in pharmaceutical substances
- Ethylene glycol and diethylene glycol in high-risk excipients

Solvent Composition / Solvent Exchange
- A.V. Mikhonin et al., *"Direct Solvent Composition Monitoring Using Headspace-MRR: Implications for Crystallization Process Optimization"*, Poster at PittCon **2025**

Today's focus

MRR Selectivity



Why MRR for Impurities

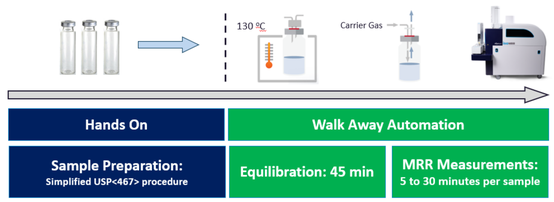
GC-Unfriendly Impurities
- ✓High-boilers from USP<467> Class 2 Mixture C solvents
- ✓EG and DEG in excipients
- ✓Small, highly-volatile species: formaldehyde, ethylene oxide, dimethyl sulfide, etc.
- ✓Water-soluble acids
- ✓Nitrosamines

Fast Analysis, Simple Workflow
- ✓No derivatization
- ✓No wait for separation
- ✓1 to 10 minutes per sample
- ✓Analytes from different standard mixtures in one run

Low Operational Costs
- ✓No mobile-phase solvents
- ✓Fully automated "push-button" analysis

Structure ID without Standards
- ✓Quasi-unknowns: unambiguous "yes" or "no" to a candidate structure (volatile NDSRI, for example)

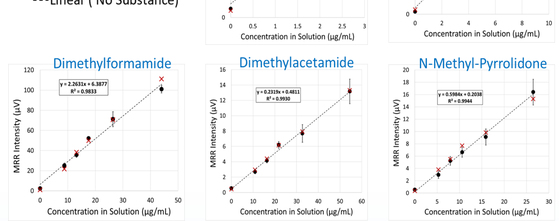
Headspace-MRR Workflow



Samples per batch: up to 66
Time to first results: about 1 hour
Analysis cycle time: 3 to 30 minutes per sample

MRR Method Validation

● No Substance
× Acetaminophen
---Linear (No Substance)



References

A.V. Mikhonin et al., "Direct Analysis of Class 2 Residual Solvents Using Molecular Rotational Resonance Spectroscopy", USP Pharmacopeial Forum, PF 51(2), March 3, 2025.

Headspace-MRR Features

- Spectroscopy, direct analysis without separation
- Unique molecular fingerprints, no spectral overlaps
- Reliable, highly-selective quantitation in mixtures
- Sensitive: no limits on headspace volumes
- Bridges analytical gaps of conventional methods
- Improves sample throughput

MRR Analysis Metrics

USP<467> Class 2 Mixture C Residual Solvent	2-Methoxyethanol	2-Ethoxyethanol	Dimethylformamide	Dimethylacetamide	N-Methylpyrrolidone	USP Pass Criteria
USP<467> Limit in substance (µg/g)	50	160	880	1090	530	
Limit in 20 mg/mL substance solution (µg/mL)	1	3.2	17.6	21.8	10.6	
Confirmed MRR Linear Range in Solution (µg/mL)	0.33 – 2.5	0.51 – 8	3.03 – 44	2.27 – 54.5	3.39 – 26.5	NLT 50-150% of USP limit
Linearity (R^2)	0.97	0.98	0.98	0.99	0.99	R^2 NLT 0.9
Repeatability (%)	8.7%	9.8%	6.2%	9.1%	11.6%	NMT 20%
Recovery in 20 mg/mL Acetaminophen (%)	96.8%	92.3%	100.8%	102.7%	109.7%	80% – 120%
Low Limit of Quantitation, LOQ, in Solution (µg/mL)	0.33	0.51	3.03	2.27	3.39	NMT 50% of USP Limit
LOQ in 20 mg/mL Acetaminophen (µg/g)	16	26	152	113	169	
MRR Metrics vs USP<467> and USP<1467> Requirements	pass	pass	pass	pass	pass	pass

Conclusions

- Reliable ID and quantitation with one instrument
- MRR can bridge analytical gaps of conventional methods
  - ❖ MRR can help with selectivity
  - ❖ MRR can help with sensitivity (use-case: low volatile analytes in injection-unfriendly matrices)
- MRR can help with analysis throughput

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